## REMARKS/ARGUMENTS

Claims 1-6 and 8-24 are pending in this application and presented for examination. In view of the Request for Continued Examination, reconsideration is respectfully requested.

## I. THE INVENTION

The present invention relates *inter alia*, to a pharmaceutical composition for topical administration comprising at least 5% by weight of a piperidinopyrimidine derivative (*e.g.*, minoxidil), or a pharmaceutically acceptable salt thereof, an acid to substantially solubilize the active agent, a solvent selected from water and/or a lower alcohol, and an aromatic or polyhydric alcohol as a co-solvent present in an amount of less than approximately 10% by weight. The acid component improves the solubility of the piperidinopyrimidine derivative in solution and thus provides compositions that are advantageous, in part, because they can contain higher concentrations of the active ingredient than are found in the compositions described in the prior art. Prior to the advent of the present invention, formulations having a large amount of a piperidinopyrimidine derivative, without concomitantly large amounts of polyols, were unknown.

## II. REJECTIONS UNDER § 103

### A. Kasting (U.S. Patent No. 5,041,439) by itself or in view of Yu (U.S. Patent No. 5,571,841) or Weiner (WO 97/12602)

The Examiner has rejected claims 1-6, 8-9, 12-19 and 21-23 as allegedly being obvious over Kasting alone, Kasting in view of Yu, or Kasting in view of Weiner. In response, Applicants respectfully traverse the rejection.

Kasting teaches minoxidil formulations with a binary surfactant system comprising a polar lipid compound selected from a $C_{16}$ mono-unsaturated alcohol, a $C_{16}$ branched chain saturated alcohol, a $C_{18}$ mono-unsaturated or a $C_{18}$ branched chain saturated

alcohol, and a small polar solvent (a $C_3$-$C_4$ diol or $C_3$-$C_6$ triol), such system improving topical delivery.

Kasting does not teach or suggest that the addition of specific amounts of acid results in a formulation having both 5% or greater minoxidil and less than 10% propylene glycol as is presently taught and claimed. Kasting in fact essentially teaches away from the present invention, as the high minoxidil concentrations of Kasting also include high concentrations of propylene glycol, or other diols or triols. Numerous other prior art formulations also teach away from the present invention by requiring high percentages of propylene glycol or a similar diol or triol to achieve high minoxidil concentrations, *i.e.* greater than 5%. (*see*, the instant specification, page 1, lines 11-21.) Thus, no suggestion or motivation has been provided to modify Kasting to arrive at a composition specifically recited in claim 1. Absent a specific suggestion or motivation to manipulate Kasting to arrive at the particular claimed combination of claim 1, a *prima facie* case of obviousness simply has not been made.

Further, Kasting teaches **avoiding** certain acids (*see*, col. 9, ln. 30-61), yet certain embodiments of the present invention have these acids that Kasting specifically teaches to avoid (*see*, claim 1, *e.g.* succinic acid). Moreover, in contrast to Kasting, the instantly claimed alcohols are lower alcohols (as the solvent) and aromatic or polyhydric alcohols (as the co-solvent). A lower alcohol is generally known in the art to be of the chain size of $C_1$-$C_6$. Aromatic alcohols would not be defined as a mono-unsaturated alcohol because they have more than one double bond (mono-unsaturated alcohol has one double bond). Aromatic alcohols would not be described as branched chain saturated alcohols, as saturated means no double bonds, and therefore is different than an aromatic alcohol which has double bonds.

Moreover, all of the examples of Kasting have very **high levels** of propylene glycol (PG) or other diols and triols (30%-97.75%). This is conventional technology that uses high propylene glycol concentrations in order to load minoxidil into the formulation. In Example II, where the PG levels are down around 10-15%, there is only 1% minoxidil in the formulation. Again, this does not teach or suggest an advantage of having both **reduced levels** of the cosolvent such as less than 10%, and **high loading of minoxidil** such as greater than 5%,

as is presently taught and claimed. Therefore, the present invention is in no way taught or suggested by Kasting.

The foregoing distinguishing comments, are further supported by the 37 C.F.R. § 1.132 declaration submitted herewith. In this regard, the Examiner's attention is respectfully directed to the accompanying 37 C.F.R. § 1.132 declaration by Mr. Barry Hunt ("the Hunt I Declaration"). Mr. Hunt is a Senior Formulation Scientist of the assignee of the subject application and has been in pharmaceutical research since 1972. He has been employed doing formulation research and development for the last 32 years.

In paragraph 9, Mr. Hunt declares that he has reviewed Kasting and as exemplified therein, formulations having high loading of minoxidil are accompanied by high levels polyhydric alcohols. If fact, in paragraph 9, Mr. Hunt sets forth that Kasting exemplifies the following formulations:

- Compositions I and XIII contain 5.0% minoxidil and 91.0% propylene glycol;
- Composition IV contains 5.0% minoxidil and 30.0% propylene glycol;
- Composition VI contains 6.0% minoxidil and 90.0% 1,2-butanediol;
- Composition XI contains 5.0% minoxidil and 92.0% 1,2-butanediol;
- Composition XIV contains 12.0% minoxidil and 54.0% 1,2,6-hexanetriol;
- Composition XVI contains 8.0% minoxidil and 55.0% 1,3-butanediol (col. 11, line 8 to col. 12, line 12).
- Compositions A-E contain 7% minoxidil and 88% to 93% propylene glycol (col. 13, lines 1-8).

Thus, Mr. Hunt declares in paragraph 9 that similar to other compositions described in the prior art, the compositions exemplified in Kasting contain a very high percentage (*i.e.*, 30% to 93%) of a polyhydric alcohol in order to improve the solubility of a high concentration (*i.e.*, at least 5%) of minoxidil. Such high amounts of polyhydric alcohol are not pharmaceutically or cosmetically elegant, may be unacceptable to the consumer, and may cause

local irritation and hypersensitivity upon application to the scalp (*see,* paragraph 7 of the Hunt I Declaration).

Further, in paragraph 11, Mr. Hunt declares that Kasting teaches that straight chain $C_4$-$C_{20}$ saturated monocarboxylic and dicarboxylic acids are capable of gross interference with penetration by the compositions described therein (col. 9, lines 47-52). However, the present invention teaches compositions wherein the acid used to substantially solubilize the piperidinopyrimidine derivative is an organic acid such as succinic acid, which is a straight chain $C_4$ saturated dicarboxylic acid (*see,* claim 1). As such, Kasting teaches away from the presently claimed compositions.

Yu does not supply the teaching that is currently lacking in the primary reference. Yu *et al.* is directed to the use of hydroxyacids to enhance the "therapeutic efficacy of cosmetic and pharmaceutical agents." (*see*, col. 2, ln. 16-21.) In particular, Yu teaches the use of "hydroxycarboxylic acids and related compounds" as "enhancing compounds" to enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders, or other afflictions. (*see*, col. 2, ln 16-42.) Yu however, is not concerned with and does not even remotely address the problem that the present invention solves, namely, increasing minoxidil amounts while minimizing amounts of propylene glycol, or other polyols. Yu clearly does not disclose or suggest the composition of claim 1, which specifically requires "at least 5% by weight" of a "piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof," "an acid in an amount to substantially completely solubilize the piperidinopyrimidine derivative or pharmaceutically acceptable salt thereof," and propylene glycol, if present at all, in an amount of "less than approximately 10% by weight."

Example 3 of Yu describes a "2% minoxidil" formulation formed by dissolving 2 grams minoxidil and 3 ml lactic acid into a mixture of 80 ml ethanol and 15 ml propylene glycol. A 2% minoxidil formulation is much less than the claimed composition which requires 5% or greater of a piperidinopyrimidine derivative, such as minoxidil. In addition, the formulation of Example 3 has a large propylene glycol content, 15%, which is substantially greater than the "less than approximately 10% by weight" of propylene glycol required by claim 1.

Weiner (WO 97/12602) does not supply the deficiencies of the primary or secondary references. Weiner teaches a formulation that requires minoxidil to be reacted with an acid or base and then be encapsulated in lipid vesicles (*see*, page 4, lns. 13-18 of Weiner). The data presented in Example 3 shows that minoxidil reacted with lactic acid, but not encapsulated in a lipid vesicle, is essentially undeliverable into hairless rat skin, whereas a lipid vesicle encapsulated lactic acid-treated minoxidil penetrated living skin strata more deeply than the other tested formulations (please compare formulations III and XI in Table 1, on page 6 in the "Living Skin Strata" col. and review the paragraph on page 7, lns. 9-17 of Weiner). Based on this data, those of skill in the art certainly would have no motivation to react minoxidil with an acid, but not encapsulate the minoxidil salt in a lipid vesicle.

In view of the foregoing, the disclosure of Kasting alone, or Kasting combined with Yu or Weiner does not teach or suggest the pharmaceutical compositions recited in independent claim 1 and dependent claims 2-6, 8-9 and 12-19 that comprise a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof and an aromatic or polyhydric alcohol co-solvent present in an amount of less than approximately 10% by weight. Similarly, Kasting alone, or Kasting combined with Yu or Weiner also does not teach or suggest methods that comprise providing a pharmaceutical composition that comprises an aromatic or polyhydric alcohol co-solvent present in an amount of less than approximately 10% by weight, as is recited in independent claim 21, and dependent claims 22-23. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

**B. Kasting (U.S. 5,041,439) by itself or in view of Yu or Weiner, and further in view of Uchikawa (U.S. 5,156,836)**

The Examiner has rejected claims 10-11, 20 and 24 by the further inclusion of Uchikawa. Claims 10-11 and 20 depend from independent claim 1, so therefore include all the limitations of claim 1. Likewise, claim 24 depends from independent 21, and includes all the limitations of claim 21. Neither claim 1 nor claim 21 have been included in this rejection.

The Examiner cites Uchikawa for disclosing benzyl alcohol as part of a long list of general purpose components and one of three potential alcohols (*see*, col. 4, lns. 7-33, especially lns. 9-11 and 31-32 of the Uchikawa patent). Uchikawa is directed to hair revitalizing tonics containing amine oxide. Uchikawa also discloses minoxidil as part of this long list of general components, but does not disclose minoxidil or any other piperidinopyrimidine derivative anywhere else, much less disclose or suggest any particular formulation having minoxidil or a piperidinopyrimidine derivative (*see*, col. 4, ln. 19).

Uchikawa considers including an amine oxide and an anionic surfactant essential to their hair tonic composition (*see*, col. 4, lns. 7-9). As claim 1 indicates, the Uchikawa hair tonic composition requires an amine oxide and an anionic surfactant (*see*, col. 11, lns. 50-53). Therefore, even in view Uchikawa, there is no teaching or suggestion of the present invention. The combined compositions proposed by the Examiner in combining Kasting, Uchikawa and Yu or Weiner are not the claimed invention. The pharmaceutical compositions recited in claims 1, 10, 11 and 20 do not require a penetration enhancer consisting of a polar solvent *and* a polar lipid alcohol, or an amine oxide and an anionic surfactant, or lipid vesicle encapsulation. The methods of treatment recited in claims 21 and 24 comprise providing a composition that does not require a penetration enhancer consisting of a polar solvent *and* a polar lipid alcohol, or an amine oxide and an anionic surfactant, or lipid vesicle encapsulation.

In view of the foregoing, the Examiner is respectfully requested to withdraw this rejection.

**C. Bazzano (U.S. 5,183,817) in view of Yu or Weiner**

The Examiner has rejected claims 1-6, 8-9, 12-19 and 21-23 as allegedly being obvious over Bazzano in view of Yu or Weiner. In response, Applicants respectfully traverse this rejection. In this regard, the Examiner's attention is respectfully directed to the accompanying 37 C.F.R. § 1.132 declaration by Mr. Barry Hunt ("the Hunt II Declaration").

Applicants submit scientific evidence showing that a skilled person would have no reasonable expectation that the claimed combination of references contemplated by the

Examiner would succeed. In fact, the combined minoxidil formulation would be insoluble, and unsuitable for topical delivery. Based upon the experiments described in the Hunt II Declaration, there would be no reasonable expectation of success of combining Bazzano with any other reference that teaches lactic acid to solubilize minoxidil.

> MPEP § 2143.02 recites:
>
> Evidence showing there was **no reasonable expectation of success** may support a conclusion of nonobviousness. [Emphasis added]. *In re Rhinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). See also, *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-1023 (Fed Cir.), cert. denied, 502 U.S. 856 (1991).

As set forth in paragraph 6, Mr. Hunt declares that Bazzano teaches a minoxidil cream containing retinoic acid, minoxidil (0.5%-5%), ethanol, propylene glycol (5-50%), and distilled water (up to 10%). Bazzano further teaches the use of a pharmaceutically acceptable salt, which is not specified (*see*, col. 19, lns. 1-25). Bazzano also discloses that a major problem in influencing hair growth is obtaining good percutaneous absorption of the active compounds, and that retinoid compounds cause excellent absorption by the hair follicles (*see*, col. 19, lns. 35-40).

Mr. Hunt declares in paragraph 7 that Yu teaches a therapeutic composition for hair loss that contains minoxidil (2%), water, ethanol, a high amount of propylene glycol (16%), and lactic acid (*see*, col. 7, Example 3). Yu also discloses the volume ratio of ethanol:water:propylene glycol to be 40:40:20 (*see*, col. 7, lns. 1-3). Although Yu teaches that lactic acid helps dissolve minoxidil (*see*, col. 7, Example 3), Yu also deems the high percentage of propylene glycol an essential component of their formulation (*see*, Examples 3 and 4; col. 7, ln. 50, bridging to col. 8 ln. 6).

Mr. Hunt declares in paragraph 8 that Weiner teaches a topical composition for minoxidil that is reacted with an acid or base and encapsulated in a lipid vesicle (*see*, page 4 ln. 13-18). Although Weiner teaches that minoxidil is modified by reacting it with an organic acid such as lactic acid (*see*, page 4, ln. 14-16), and that making materials more hydrophilic improves

penetration through the hair follicle (*see*, page 4, ln. 5-10), Weiner also teaches that minoxidil reacted with lactic acid, but not encapsulated in a lipid is essentially undeliverable into hairless rat skin (*see*, Example 3 in Weiner).

In paragraph 9, Mr. Hunt declares that Uchikawa teaches a hair tonic that contains a long list of general purpose components and one of three potential alcohols including benzyl alcohol (*see*, col. 4 lns. 7-33, especially lns. 9-11 and 31-32). In addition, Uchikawa considers including an amine oxide and an anionic surfactant essential to their formulation, (*see*, col. 4, lns. 7-9), but does not consider minoxidil an essential component to their formulation.

As Mr. Hunt declares in paragraph 10, "...it is my scientific understanding that Weiner and Yu teach very different formulations than is currently claimed, and the use of lactic acid to improve the solubility and absorptive efficacy of the minoxidil compound, respectively. Bazzano, however, teaches that the synergism afforded by retinoic acid and minoxidil are required for effective treatment of advanced alopecia."

As declared in paragraph 12, it is Mr. Hunt's scientific opinion that supplementing the teaching of Bazzano with the teaching of Yu or Weiner does not lead to a reasonable expectation of success. In fact, he performed experiments based on the amounts of lactic acid that have been used to help solubilize minoxidil to determine the solubilizing effect of lactic acid on retinoic acid to simulate the combination of teachings of Bazzano with Yu or Weiner.

In a set of experiments, (*see*, paragraph 13), he tested the solubility of a 0.1% retinoic acid in a water solution containing lactic acid in various amounts: 0, 1.0, 2.5, 5.0, and 10%. The amount of retinoic acid dissolved in solution was observed using a visual method as well as determined by UV absorbance. The results of these tests show that the solubility of retinoic acid is negligible in water. The solubility was not enhanced by the addition of lactic acid. Nor was the solubility enhanced when the lactic acid solution was neutralized to a pH similar to the pH used for solubilizing minoxidil. He determined that at 0%, 1%, 2.5%, 5.0%, and 10% lactic acid, the amount of dissolved retinoic acid was less than 0.00005%! (*see*, paragraph 13).

Mr. Hunt declares in paragraph 14 that:

> [i]t is my scientific opinion **that the suggested combination would not work** due to the insolubility of retinoic acid in the presence of lactic acid. We have conducted experiments showing that the solubility of retinoic acid is negligible in water. The solubility was not enhanced by the addition of lactic acid. Nor was the solubility enhanced when the lactic acid solution was neutralized to a pH similar to that used for solubilizing minoxidil. [Emphasis added].

Therefore, the combined disclosures of Bazzano and Yu or Bazzano and Weiner can not properly render claims 1-6, 8-9, 12-19 and 21-23 obvious. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

**D. Bazzano in view of Yu or Weiner, and further in view of Uchikawa**

The Examiner has rejected claims 10-11, 20 and 24 by the further inclusion of Uchikawa.

For the reasons analogous to those submitted above, there would be no reasonable expectation that the combined disclosures of Bazzano, Yu or Weiner and Uchikawa would succeed. This is based on the scientific evidence that the retinoic acid/lactic acid formulations are insoluble. Again, Mr. Hunt declares in paragraph 14 that

> [i]t is my scientific opinion **that the suggested combination would not work** due to the insolubility of retinoic acid in the presence of lactic acid. We have conducted experiments showing that the solubility of retinoic acid is negligible in water. The solubility was not enhanced by the addition of lactic acid. Nor was the solubility enhanced when the lactic acid solution was neutralized to a pH similar to that used for solubilizing minoxidil. [Emphasis added].

Further in paragraph 16, Mr. Hunt declares that "the teachings of Uchikawa, which the Examiner uses to teach the use of benzyl alcohol, would still not lead to a reasonable expectation of success. It is my scientific opinion that at best, benzyl alcohol would only marginally increase the solubility of retinoic acid in the lactic acid solutions tested and described above."

In view of the foregoing, the Examiner is respectfully requested to withdraw this rejection.

**E. Navarro (WO 97/03638) in view of Weiner**

The Examiner has rejected claims 1-6, 8-9, 12-19 and 21-23 as allegedly being obvious over Navarro in view of Weiner. In view of the Declaration by Abram submitted concurrently herewith, Applicants respectfully traverse this rejection.

Under MPEP § 2143.01, in making a *prima facie* case of obviousness, the Examiner's proposed modification **cannot** render the prior art unsatisfactory for its intended purpose.

> If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, **then there is no suggestion or motivation to make the proposed modification**.[Emphasis added] *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

In this regard, the Examiner's attention is respectfully directed to the accompanying 37 C.F.R. § 1.132 declaration by Mr. Albert Zorko Abram[1]. Mr. Abram declares in paragraph 9, that it is his scientific opinion that supplementing the teaching of Navarro with the teaching of Weiner **would destroy** the intended purpose of the Navarro composition. Navarro discloses the addition of γ-cyclodextrin to a minoxidil composition to improve the solubility of minoxidil in solution and also to improve the cosmetic touch properties of the solution when applied to hair and skin.

He continues in paragraph 10 by declaring that the role of cyclodextrin in Navarro is to function as a host molecule to trap the minoxidil "guest" molecule inside the ring. It is this minoxidil-cyclodextrin "host-guest" complex that imparts improved solubility properties, as compared to a similar minoxidil composition not having cyclodextrin. (See, highlighted sections of Appendix 1, Morrison & Boyd, *Organic Chemistry*, 5th ed., 1987.) The glycosidic bonds in

[1] This declaration by Mr. Albert Zorko Abram was first submitted in U.S. Application No. 10/124,197, on June 18, 2004.

cyclodextrin are **acid labile** and it is a scientific fact that subjecting cyclodextrins to acidic conditions will result in the degradation of the cyclodextrins into its individual glucose units. Thus, it is recognized that cyclodextrins are **unstable in acidic conditions** (see, highlighted sections of Appendix 2, Ullmann's Encyclopedia of Industrial Chemistry, Copyright © 2002 by Wiley-VCH Verlag GmbH & Co.). Weiner discloses a minoxidil composition having an acid component.

Again, under MPEP § 2143.01, if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, **then there is no suggestion or motivation to make the proposed modification**. It is Mr. Abram's scientific opinion that the addition of an acid, as taught by Weiner to the composition of Navarro, would result in the degradation of the cyclodextrin ring and thus **destroy** the purpose of Navarro's invention. (Please see paragraph 10.)

Accordingly, the Examiner's obviousness rejection has been obviated. Therefore, it is respectfully requested that this rejection be withdrawn.

**F. Navarro in view of Weiner, and further in view of Uchikawa**

The Examiner has rejected claims 10-11, 20 and 24 by the further inclusion of Uchikawa. Applicants respectfully traverse the rejection.

As discussed above, under MPEP § 2143.01, if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, **then there is no suggestion or motivation to make the proposed modification**. It is Mr. Abram's scientific opinion that the addition of an acid, as taught by Weiner to the composition of Navarro, would result in the degradation of the cyclodextrin ring and thus **destroy** the purpose of Navarro's invention. (Please see paragraph 10.) Cyclodextrins are **unstable in acidic conditions** (see, highlighted sections of Appendix 2, Ullmann's Encyclopedia of Industrial Chemistry, Copyright © 2002 by Wiley-VCH Verlag GmbH & Co.). Weiner discloses a minoxidil composition having an acid component. As such, the purpose of the primary reference of Navarro when combined with the teaching of Weiner is destroyed.

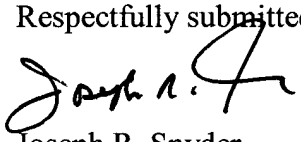
The further inclusion of Uchikawa does not make the proposed modification suitable for its intended purpose. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

## III. Conclusion

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachments
JS:jc
60274742 v1

PATENT
Attorney Docket No.: 021706-000800US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Tony Wai-Chiu So *et al.*

Application No.: 09/673,872

Filed: December 4, 2000

For: PHARMACEUTICAL COMPOSITION

Customer No.: 20350

Confirmation No. 5826

Examiner: Sharmila S. Gollamudi

Technology Center/Art Unit: 1616

DECLARATION UNDER 37 C.F.R. § 1.132

DECLARATION I OF BARRY HUNT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Barry Hunt, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true.

2. I am currently employed by Connetics Australia Pty Ltd, the assignee of the subject application.

3. I am a Formulation Scientist and have been in pharmaceutical research since 1972. I have been doing formulation research and development for the last 32 years. My *Curriculum Vitae* is attached as Exhibit A.

4. I have reviewed and analyzed the above-referenced patent application, and I am familiar with the contents therein. In addition, I have read the Office Action dated May 14, 2004, received in the present case, and I have reviewed the references cited therein by the Examiner.

5. It is my understanding that the Examiner has rejected claims 1-6, 8-9, 12-19, and 21-23 as allegedly being obvious over Kasting (U.S. Patent No. 5,041,439) by itself or in view of Yu (U.S. Patent No. 5,571,841) or Weiner (WO 97/12602). Further, it is my understanding that the Examiner has rejected claims 10-11, 20, and 24 as allegedly being obvious over Kasting by itself or in view of Yu or Weiner, and further in view of Uchikawa (U.S. Patent No. 5,156,836). For the reasons set forth herein, the Examiner's concerns are overcome.

6. The present invention relates to pharmaceutical compositions for topical administration comprising at least 5% by weight of a piperidinopyrimidine derivative (*e.g.*, minoxidil) or a pharmaceutically acceptable salt thereof, an acid to substantially solubilize the active agent, a solvent selected from water and/or a lower alcohol, and a co-solvent selected from an aromatic and/or polyhydric alcohol (*e.g.*, propylene glycol) present in an amount of less than approximately 10% by weight.

7. The compositions described in the prior art typically require a very high percentage (*e.g.*, 30% to 50%) of a polyhydric alcohol in order to improve the solubility of a high concentration (*e.g.*, at least 5%) of minoxidil. However, such high amounts of polyhydric alcohol are not pharmaceutically or cosmetically elegant, may be unacceptable to the consumer, and may cause local irritation and hypersensitivity upon application to the scalp (*see,* page 1, lines 11-21 of the instant application).

8. Kasting teaches minoxidil compositions with a penetration-enhancing vehicle containing a polyhydric alcohol selected from a $C_3$-$C_4$ diol or a $C_3$-$C_6$ triol and a polar lipid compound selected from a $C_{16}$ or $C_{18}$ mono-unsaturated or branched chain saturated alcohol (col. 4, lines 26-35).

9. Although Kasting exemplifies compositions containing at least 5% minoxidil, such compositions contain a very high percentage (*i.e.*, 30% to 93%) of a polyhydric alcohol. For example, Compositions I and XIII contain 5.0% minoxidil and 91.0% propylene glycol; Composition IV contains 5.0% minoxidil and 30.0% propylene glycol; Composition VI contains 6.0% minoxidil and 90.0% 1,2-butanediol; Composition XI contains 5.0% minoxidil and 92.0% 1,2-butanediol; Composition XIV contains 12.0% minoxidil and 54.0% 1,2,6-hexanetriol; and Composition XVI contains 8.0% minoxidil and 55.0% 1,3-butanediol (col. 11, line 8 to col. 12, line 12). Likewise, Compositions A-E contain 7% minoxidil and 88% to 93% propylene glycol (col. 13, lines 1-8). As such, similar to other compositions described in the prior art, the compositions exemplified in Kasting contain a very high percentage (*i.e.*, 30% to 93%) of a polyhydric alcohol in order to improve the solubility of a high concentration (*i.e.*, at least 5%) of minoxidil. Moreover, Kasting further teach the use of a polar lipid compound selected from a $C_{16}$ or $C_{18}$ mono-unsaturated or branched chain saturated alcohol.

10. In stark contrast, the present invention teaches compositions comprising at least 5% by weight of a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof, an acid to substantially solubilize the active agent, a solvent selected from water and/or a lower alcohol, and an aromatic and/or polyhydric alcohol present in an amount of ***less than approximately 10%*** by weight. As a result, the amount of polyhydric alcohol in the compositions of the present invention is at least 3-fold lower than the amount found in the high (*i.e.*, at least 5%) minoxidil compositions described in Kasting. In particular, the compositions of the present invention contain substantially lower concentrations of polyhydric alcohol because the acid component advantageously improves the solubility of the piperidinopyrimidine derivative. As such, the use of an acid to solubilize at least 5% of a piperidinopyrimidine derivative, instead of the use of a very high percentage of a polyhydric alcohol as exemplified by Kasting, circumvents the above-described disadvantages associated with a very high polyhydric alcohol concentration.

11. In addition, Kasting teaches that straight chain $C_4$-$C_{20}$ saturated monocarboxylic and dicarboxylic acids are capable of gross interference with penetration by the compositions described therein (col. 9, lines 47-52). However, the present invention teaches compositions wherein the acid used to substantially solubilize the piperidinopyrimidine derivative is an organic acid such as succinic acid, which is a straight chain $C_4$ saturated dicarboxylic acid (*see*, claim 1). As such, Kasting teaches away from the presently claimed compositions.

12. For these reasons, I believe that the present invention is not rendered obvious by Kasting.

The declarant has nothing further to say.

Barry Hunt

16/8/2004

Date

60279001 v1

connetics australia pty ltd

# Curriculum Vitae

## Barry Hunt

Barry Hunt was educated initially in England and received his tertiary education at Caulfield Technical College (now Monash University, Caulfield Campus).

He worked for Ensign Laboratories in Melbourne for nearly 30 years as a Development Chemist. During this time he developed and worked on a range of applications, including aerosols, personal care, pharmaceuticals, household and industrial products.

For the last twenty years he has also run a small consulting business, giving advice to manufacturers and marketers and making small pilot scale and production batches of creams and lotions.

Five years ago he moved to Soltec Research as a Senior Research Scientist. At the time Soltec was part of the FH Faulding group, and was purchased in April 2001 by Connetics Corporation in San Francisco, California. In October 2002 the company was re-named "Connetics Australia". Connetics Corporation is a marketer of topical products to the Dermatology field in the USA, and Connetics Australia is the R&D arm of this rapidly developing enterprise. Barry is a Senior Formulation Scientist and is part of a team of a dozen scientists actively engaged in developing innovative delivery platforms and technologies for the skin care industry.

He has been active on ASCC committees and the Council, and served as President of the ASCC for two years. He is a life member of the ASCC.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

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On 8/16/04

TOWNSEND and TOWNSEND and CREW LLP

By: Judith Cotta

PATENT
Attorney Docket No.: 021706-000800US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re application of: | Confirmation No. 5826 |
| Tony Wai-Chiu So *et al.* | Examiner: Sharmila S. Gollamudi |
| Application No.: 09/673,872 | Technology Center/Art Unit: 1616 |
| Filed: December 4, 2000 | DECLARATION II OF BARRY HUNT |
| For: PHARMACEUTICAL COMPOSITION | |
| Customer No.: 20350 | |

I, Barry Hunt, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I am currently employed by Connetics Australia Pty Ltd, the assignee of the subject application.

3. I am a Senior Formulation Scientist and have been in pharmaceutical research since 1972. I have been employed doing formulation research and development for the last 32 years. My *Curriculum Vitae* is attached as Exhibit A in Declaration I.

4. I have read and I am familiar with the contents of the above-referenced patent application. In addition, I have read the Final Office Action dated May 14, 2004, received

from the Patent Office in connection with the above-referenced application. It is my understanding that the Examiner alleges that claims 1-6, 8-9, 12-19, and 21-23 of the present invention are obvious over Bazzano (U.S. 5,183,817) in view of Yu (U.S. 5,571,841) or Weiner (WO 97/12602). Furthermore the Examiner alleges that claims 10-11, 20 and 24 are obvious over Bazzano in view of Yu or Weiner in further view of Uchikawa (U.S. 5,156,836). For the reasons set forth herein, the Examiner's concerns are overcome.

5. The present invention relates to a pharmaceutical composition for topical administration comprising at least 5% by weight a piperidinopyrimidine derivative (*e.g.*, minoxidil), or a pharmaceutically acceptable salt thereof, an acid to substantially solubilize the active agent, a solvent selected from water and/or a lower alcohol, and an aromatic and polyhydric alcohol as a co-solvent present in an amount of less than approximately 10% by weight. The acid component improves the solubility of the piperidinopyrimidine derivative in solution and thus provides compositions that are advantageous, in part, because they can contain higher concentrations of the active ingredient than are found in the compositions described in the prior art.

6. Bazzano teaches a minoxidil cream containing retinoic acid, minoxidil (0.5%-5%), ethanol, propylene glycol (5-50%), and distilled water (up to 10%). Bazzano further teaches the use of a pharmaceutically acceptable salt, which is not specified (column 19, lines 1-25). Bazzano also discloses that a major problem in influencing hair growth is obtaining good percutaneous absorption of the active compounds, and that retinoid compounds cause excellent absorption by the hair follicles (column 19, lines 35-40). The Bazzano formulation requires a retinoid to aid in percutaneous absorption of minoxidil, because "neither compound [minoxidil or a retinoid] alone may have profound effects on advanced alopecias." See, column 5, lines 16-29; Table II and corresponding analysis in column 23, line 34 through column 24, line 5 of the Bazzano patent.

7. Yu teaches a therapeutic composition for hair loss that contains minoxidil (2%), water, ethanol, a high amount of propylene glycol (16%), and lactic acid (column 7,

Example 3). Yu also discloses the volume ratio of ethanol:water:propylene glycol to be 40:40:20 (column 7, lines 1-3). Although Yu teaches that lactic acid helps dissolve minoxidil (column 7, Example 3), Yu also deems the high percentage of propylene glycol an essential component of their formulation (Examples 3 and 4; column 7, line 50, bridging to column 8 line 6).

8. Weiner teaches a topical composition for minoxidil that is reacted with an acid or base and encapsulated in a lipid vesicle (page 4 line 13-18). Although Weiner teaches that minoxidil is modified by reacting it with an organic acid such as lactic acid (page 4, line 14-16), and that making materials more hydrophilic improves penetration through the hair follicle (page 4, line 5-10), Weiner also teaches that minoxidil reacted with lactic acid, but not encapsulated in a lipid is essentially undeliverable into hairless rat skin (Example 3 in Weiner publication).

9. Uchikawa teaches a hair tonic that contains a long list of general purpose components and one of three potential alcohols including benzyl alcohol (column 4 lines 7-33, especially lines 9-11 and 31-32). In addition, Uchikawa considers including an amine oxide and an anionic surfactant essential to their formulation, (column 4, lines 7-9), but does not consider minoxidil an essential component to their formulation.

10. Thus, it is my scientific understanding that Weiner and Yu teach very different formulations than is currently claimed, and the use of lactic acid to improve the solubility and absorptive efficacy of the minoxidil compound, respectively. Bazzano, however, teaches that the synergism afforded by retinoic acid and minoxidil are required for effective treatment of advanced alopecia.

11. It is my understanding that the Examiner alleges that the present claims, by reciting "comprising," do not exclude the possibility of having a minoxidil formulation having both lactic acid and retinoic acid, and as such, the present claims are rendered obvious by Bazzano in view of Yu or Weiner. I respectfully disagree with the Examiner on this point based on scientific evidence.

12. Based on my experiments, as detailed below, it is my scientific opinion that supplementing the teaching of Bazzano with the teaching of Yu or Weiner does not lead to a reasonable expectation of success. I performed experiments based on the amounts of lactic acid that have been used to help solubilize minoxidil to determine the solubilizing effect of lactic acid on retinoic acid to simulate the combination of teachings of Bazzano with Yu or Weiner. My laboratory notebook page numbers 20-23 are attached as an Exhibit.

13. In a set of experiments, (laboratory notebook pages 20-23[1]), I tested the solubility of a 0.1% retinoic acid in a water solution containing lactic acid in the following amounts: 0%, 1.0%, 2.5%, 5.0%, and 10%. The amount of retinoic acid dissolved in solution was observed using a visual method as well as determined by UV absorbance. The results of these tests show that the solubility of retinoic acid is negligible in water. The solubility was not enhanced by the addition of lactic acid. Nor was the solubility enhanced when the lactic acid solution was neutralized to a pH similar to the pH used for solubilizing minoxidil. I determined that at 0%, 1%, 2.5%, 5.0%, and 10% lactic acid, the amount of dissolved retinoic acid was less than 0.00005%!

14. Bazzano discloses the synergism of retinoic acid with minoxidil, while Yu or Weiner disclose the use of lactic acid to increase the solubility and absorption of minoxidil. Combining the references requires a formulation containing both retinoic acid and lactic acid with minoxidil. It is my scientific opinion that the suggested combination would not work due to the insolubility of retinoic acid in the presence of lactic acid. We have conducted experiments showing that the solubility of retinoic acid is negligible in water. The solubility was not enhanced by the addition of lactic acid. Nor was the solubility enhanced when the lactic acid solution was neutralized to a pH similar to that used for solubilizing minoxidil.

15. Based upon my experiments, there would be no expectation of success of combining Bazzano with any other reference that teaches lactic acid to solubilize minoxidil.

[1] The dates have been redacted.

16. The teachings of Uchikawa, which the Examiner uses to teach the use of benzyl alcohol, would still not lead to a reasonable expectation of success. It is my scientific opinion that at best, benzyl alcohol would only marginally increase the solubility of retinoic acid in the lactic acid solutions tested and described above.

17. For these reasons, I believe that the present invention is not rendered obvious by the combination of Bazzano in view of Yu or Weiner, or in further view of Uchikawa.

18. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true and further that these statement are made with the knowledge that willful false statements and the like so made may jeopardized the validity of the application or any patent issuing thereon.

Barry Hunt — Date 16/8/2004

E241/3 contd Date 1/1/

from p-12

## Combination of Tretinoin/Lactic

New tests:

Aim:

**Minoxidil Patent – tretinoin testing**
Barry Hunt

**Proposed tests**

Based on the amounts of lactic acid that have been used to help solubilise minoxidil, the following tests are suggested to demonstrate solubilising effect (or lack of same) of lactic acid on retinoic acid (tretinoin). With 5% minoxidil, 1% and 5% lactic acid gave a pH of 4.15 and 2.79 respectively. The percentages below are calculated in the final solution, and not as a percentage of lactic acid in tretinoin or vice-versa.

Tretinoin level – 0.1%
Lactic acid level – 0, 1.0, 2.5, 5.0, 10.0%.

**Procedure**

Weigh the appropriate amount of lactic acid into a 120mL jar and make up to 50g with water. Repeat to give the five levels of lactic acid above.

Add 0.050g +/- 0.002g of tretinoin to each jar, fit cap, and mix on magnetic stirrer for 30 minutes.

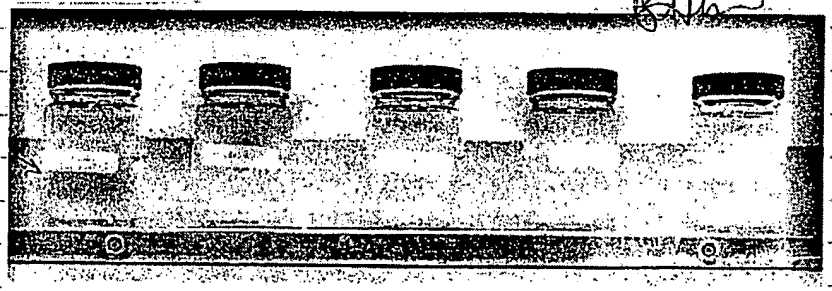
Allow to settle until clear liquid is clearly visible. Assess the tretinoin level dissolved in the liquid by comparing the colour of the clear liquid with a range of samples containing known amounts of tretinoin in ethanol/water solutions. If this method appears to be unreliable or inaccurate we will use UV spectrophotometry or HPLC.

If any solubility of tretinoin in the lactic acid solutions is detected, the pH will be raised with sodium hydroxide solution to pH 5.0 – 5.5, and the solubility measured again by the same method used above.

*Notes for visual method. Diluting 0.1% tretinoin 1 in 100 with an ethanol-water mixture (about 20/80) gives a pale but visible yellow colour. This is 0.001% or 10mg/L. The same concn in pure ethanol is colourless.*

*Notes for UV method (ex Eur Ph). Tretinoin absorbs at 353nm, concn. 3.75mg/L. Specific absorbance 1500. Isotretinoin at 354nm. Spec abs 1350. Solvent acidified isopropanol (1mL 0.01M HCl/litre).*

Lactic acid is ~ 90% so use ~ 10% more.
So 0, 1.1, 2.75, 5.5, 11%.
or actual 0, 0.55g, 1.38g, 2.8g, 5.5g
up to 50g with water.



0% lactic looks darker yellow with tint

| | |
|---|---|
| Recorded by: | Date: |
| Witnessed & Understood by: | Date: |
| Connetics Australia Pty Ltd | |

EJ441/3 contd

late 1/1 contd

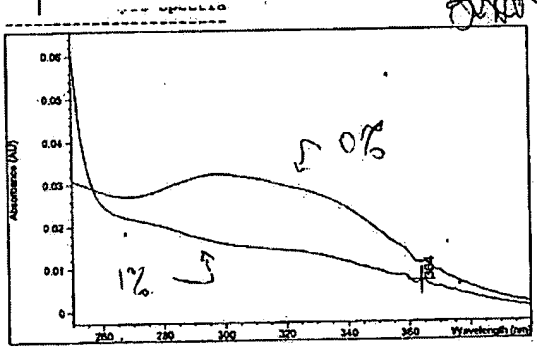
Tretinoin/Lactic

After ~ 1h stirring turn off & leave standing for a while.

0% lactic looks v. yellow but this may be suspended yellow particles of tretinoin. The higher density of the lactic soln. may be why they appear to be clearer, with powder floating on top.

After settling longer the 0% lactic still has yellowish hue.

Take blank, a pass through syringe filter into 1 cm quartz cell. Water as blank. There is a v. small peak at 297 nm, melting visible at ~350 (known peak for tretinoin). Run the 1% lactic sample.




Both are v. low absorbances. Neither show any peak typical of tretinoin.
Soln. of 0.005% tretinoin in EtOH/water is way off scale >> 4.
0.001% in EtOH, 1.04 at 350 nm.

Recorded by: Date: 1/11/
Witnessed & Understood by: Date: /
Connetics Australia Pty Ltd

F241/3 cont'd

Given Abs. of 1.04 for 0.001% tetracaine the absorbances seen in the water/lactic samples are corresponding to less than 0.0000 5% tetracaine (Abs << 0.05).

Place each soln. on pH meter in turn & add 20% NaOH soln. until pH is 5.0 - 5.5, except for water, 0% lactic.

| | | | |
|---|---|---|---|
| 1% | pH | 2.30 → 5.10 | ~ 20 drops. |
| 2.5% | | 2.15 → 5.08 | Sl. < 2 mL |
| 5% | | 2.00 → 5.09 | Sl. < 4 mL. |
| 10% | | 1.85 → 5.09 | ~ 7 mL |

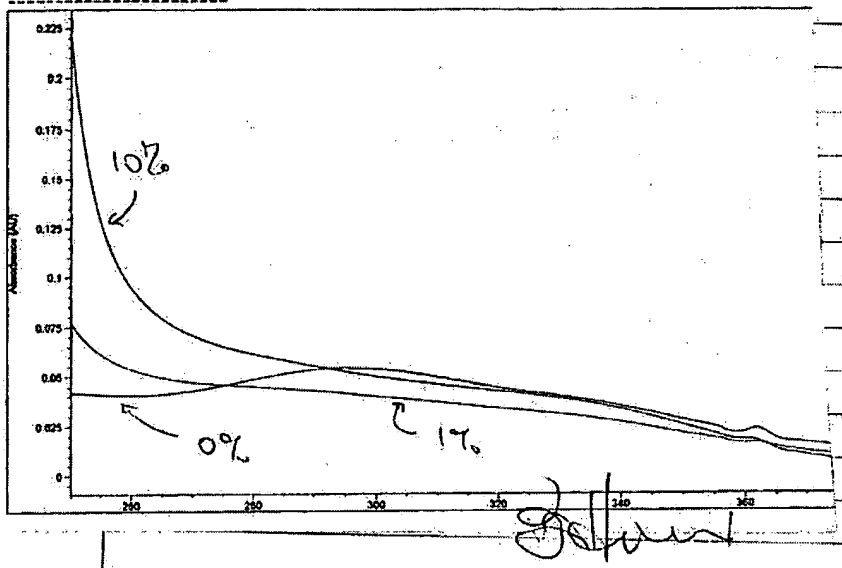
Leave stirring for at least 30 min then stand o/night.

Connetics Australia Pty Ltd

Ex 41/3 contd Date 1.4

Tretinoin/lactic

After standing o/night, all are clear + colourless. To check, run uv on 0, 1 + 10% samples, vs. water.




Negligible absorption at 350 nm. As for earlier samples, Abs. indicates < 0.00005% tretinoin dissolved.

Conclusion: solubility of retinoic acid/tretinoin in water is extremely low. Solubility is not enhanced by addition of lactic acid. Solubility is not enhanced when the lactic acid solutions are neutralised to a pH similar to that used in solubilising minoxidil. As the solubility was so low, there was no point in testing the stability of the retinoic acid in this system.

Recorded by: Date: 1.4.02

Witnessed & Understood by: Date:

Connetics Australia Pty Ltd

PATENT
Attorney Docket No.: 021706-000810US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re application of: | Confirmation No. 1659 |
| Tony Wai-Chiu So *et al.* | Examiner: Sharmila S. Gollamudi |
| Application No.: 10/124,197 | Technology Center/Art Unit: 1616 |
| Filed: April 16, 2002 | DECLARATION |
| For: PHARMACEUTICAL COMPOSITION | |

I, Albert Zorko Abram, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I am currently employed by Connetics Australia Pty Ltd, the assignee of the subject application.

3. I am a Senior Chemist-Technical IP Associate and have been in pharmaceutical research since 1987. I have been employed doing dermatological product development for the last 16 years. My *Curriculum Vitae* is of record.

4. I have read and I am familiar with the contents of the above-referenced patent application. In addition, I have read the Office Action dated October 17, 2003 and the Advisory Action dated February 17, 2004 received from the Patent Office in connection with the above-referenced application. It is my understanding that the Examiner alleges that the claimed invention is obvious in view of the disclosures of Navarro (WO 97/03638) in view of Weiner (WO 97/12602), in further view of Leitch (U.S. Patent No. 5,753,216). More particularly, it is my understanding that the Examiner alleges that Navarro discloses a minoxidil composition comprising:

a) 0.1 to 3% by weight of minoxidil;
b) 0.1-3% by weight of a γ-cyclodextrin;
c) 0.5-15% by weight of a solvent; and
d) 30-50% by weight of a monoalcohol.

However, the Examiner admits that Navarro does not teach or suggest the addition of an acid, as is instantly claimed, but this deficiency is supplemented by the disclosure of Weiner (WO 97/03638). Weiner allegedly describes modifying the solubility of a therapeutic material by adding an acid. The Examiner alleges that since Weiner describes the addition of an acid to a minoxidil solution, it would have been obvious to combine the teaching of Navarro with Weiner, in view of Leitch to arrive at the presently claimed invention. Leitch was cited by the Examiner as showing that aerosols are known in the hair care art.

5. The fundamental basis of the Navarro composition is the inclusion of a γ-cyclodextrin compound, which acts to improve the solubility of minoxidil and the cosmetic touch properties of the hair and skin areas to which the minoxidil solution is applied.

6. The present invention relates to a homogeneous aerosol composition comprising:

> a) 5% or greater of a piperidinopyrimidine derivative (e.g., minoxidil)
>
> b) **an acid** selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, citric acid, acetic acid, succinic acid, maleic acid, benzoic acid, lactic acid and mixtures thereof;
>
> c) a solvent of water and a lower alcohol in a ratio of 1:9 to 9:1 by volume;
>
> d) a co-solvent of a polyhydric alcohol selected from 1,3-butylene glycol, polyethylene glycol, hexylene glycol, dipropylene glycol, glycerol or propylene glycol at less than approximately 10% by weight;
>
> wherein the final product of the homogeneous aerosol formulation is a foam or mousse.

The addition of **an acid** to the instantly claimed composition is a critical feature of the present invention as it is the acid component that improves the solubility of the piperidinopyrimidine derivative (e.g., minoxidil) in solution and thus provides compositions that are advantageous, in part, because they can contain higher concentrations of the active ingredient (e.g., minoxidil) than are found in the compositions described in the prior art.

7. The Examiner further alleges, in regard to the obviousness rejection over Navarro in view of Weiner and Leitch that since the instant claims contain open language, the claims do not exclude additional components, such as lipid vesicles, to the composition (see, Advisory Action dated February, 17, 2004, page 3, lines 3-5). Following this logic, it is my understanding that the Examiner alleges that the present claims, by reciting "comprising," does

not exclude the possibility of having a cyclodextrin compound, and as such, the present claims are rendered obvious by Navarro in view of Weiner and further in view of Leitch. I respectfully disagree with the Examiner on this point.

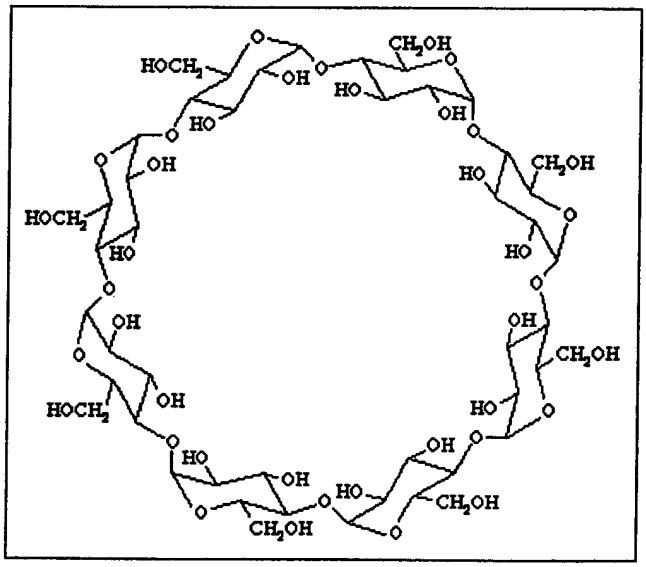
8. According to MPEP § 2143.01, in making a *prima facie* case of obviousness, the Examiner's proposed modification **cannot** render the prior art unsatisfactory for its intended purpose.

> MPEP § 2143.01:
> If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, **then there is no suggestion or motivation to make the proposed modification.**[Emphasis Added] *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

9. It is my scientific opinion that supplementing the teaching of Navarro with the teaching of Weiner **would destroy** the intended purpose of the Navarro composition. Navarro discloses the addition of γ-cyclodextrin to a minoxidil composition to improve the solubility of minoxidil in solution and also to improve the cosmetic touch properties of the solution when applied to hair and skin.

10. Cyclodextrins are polysaccharide molecules consisting of D-glucose units that are linked through glycosidic bonds to form a ring. In particular, γ-cyclodextrin is made up of eight glucose units.

γ-Cyclodextrin



The role of cyclodextrin in Navarro is to function as a host molecule to trap the minoxidil "guest" molecule inside the ring. It is this minoxidil-cyclodextrin "host-guest" complex that imparts improved solubility properties, as compared to a similar minoxidil composition not having cyclodextrin. (see, highlighted sections of Appendix 1, Morrison & Boyd, *Organic Chemistry*, 5th ed., 1987). The glycosidic bonds in cyclodextrin are **acid labile** and it is a scientific fact that subjecting cyclodextrins to acidic conditions will result in the degradation of the cyclodextrins into its individual glucose units. Thus, it is recognized that cyclodextrins are **unstable in acidic conditions** (see, highlighted sections of Appendix 2, Ullmann's Encyclopedia of Industrial Chemistry, Copyright © 2002 by Wiley-VCH Verlag GmbH & Co.). Weiner discloses a minoxidil composition having an acid component. It is my scientific opinion that the addition of an acid, as taught by Weiner to the composition of Navarro, would result in the degradation of the cyclodextrin ring and thus **destroy** the purpose of Navarro's invention.

11. For these reasons, I believe that the present invention is not rendered obvious by the disclosure of Navarro in view of Weiner, further in view of Leitch. The teaching of Leitch in no way supplements the deficiencies of Navarro in view of Weiner.

12. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true and further that these statement are made with the knowledge that willful false statements and the like so made may jeopardized the validity of the application or any patent issuing thereon.

Albert Zorko Abram

8th June, 2004
Date

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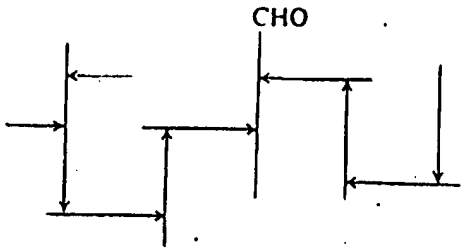


Amylopectin

Glycogen, the form in which carbohydrate is stored in animals to be released upon metabolic demand, has a structure very similar to that of amylopectin, except that the molecules appear to be more highly branched, and to have shorter chains (12–18 D-glucose units each).

**Problem 39.16** Polysaccharides known as *dextrans* have been used as substitutes for blood plasma in transfusions; they are made by the action of certain bacteria on (+)-sucrose. Interpret the following properties of a dextran: Complete hydrolysis by acid yields only D-(+)-glucose. Partial hydrolysis yields only one disaccharide and only one trisaccharide, which contain only $\alpha$-glycoside linkages. Upon methylation and hydrolysis, there is obtained chiefly 2,3,4-tri-*O*-methyl-D-glucose, together with smaller amounts of 2,4-di-*O*-methyl-D-glucose and 2,3,4,6-tetra-*O*-methyl-D-glucose.

**Problem 39.17** Polysaccharides called *xylans* are found along with cellulose in wood and straw. Interpret the following properties of a sample of xylan: Its large negative rotation suggests $\beta$ linkages. Complete hydrolysis by acids yields only D-(+)-xylose. Upon methylation and hydrolysis, there is obtained chiefly 2,3-di-*O*-methyl-D-xylose, together with smaller amounts of 2,3,4-tri-*O*-methyl-D-xylose and 2-*O*-methyl-D-xylose.

## 39.10 Cyclodextrins

When starch is treated with a particular enzyme (the amylase of *Bacillus macerans*), there is formed a mixture of *cyclodextrins*: polysaccharides of low molecular weight belonging to the general class called *oligosaccharides* (*oligo* = few).

A cyclodextrin consists of six, seven, eight, or more D-glucose units joined through 1,4-*alpha* linkages in such a way as to form a ring—a chain bracelet each link of which is a pyranose hexagon. These rings are doughnut-shaped, much as crown ethers are (Sec. 19.10), but with a number of important differences. The smallest of them, $\alpha$-cyclodextrin, has a diameter about twice that of 18-crown-6, and its hole (4.5 Å across) is about twice as broad.

This hole is tapered slightly, so that the molecule is shaped like a tiny pail with the bottom knocked out (see Fig. 39.4, on the next page). Making up the sides is a loop of six or more hexagons, each one lying roughly in the plane of the sides; the depth of the pail is thus the width of the pyranose ring. Outside the pail, around the "upper", larger rim lie the secondary —OH groups of C-2 and C-3; around the "lower", smaller rim lie the primary —OH groups of C-6, that is, the $-CH_2OH$ groups. The inside of the pail consists of three bands, one on top of another: two bands of C—H's and, in between, a band of glycosidic O's.

Like a crown ether, a cyclodextrin can act as a host to guest molecules. Indeed, it was in connection with this property of cyclodextrins that the phenomenon now

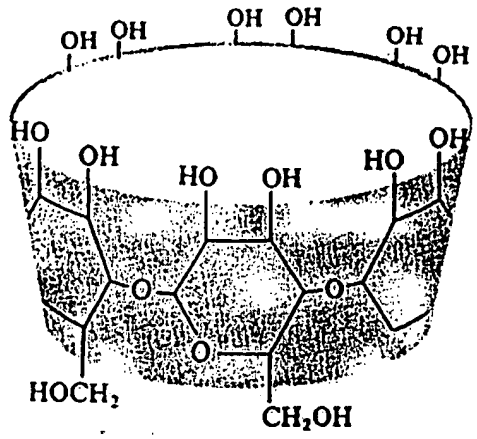


Figure 39.4 A schematic representation of α-cyclodextrin. The secondary —OH groups face outward about the "upper" rim; the $-CH_2OH$ groups face outward about the "lower" rim. The cavity is lined with C—H's and glycosidic O's in three bands lying one above another.

known as the host–guest relationship was first recognized. But, in contrast to a crown ether, a cyclodextrin has a polar, hydrophilic outside and a relatively non-polar lipophilic inside. This leads naturally to two important results: (a) into its lipophilic interior a cyclodextrin typically takes as a guest, not an ion, but a non-polar organic molecule or the non-polar end of an organic molecule; and (b) its hydrophilic exterior confers water solubility on the resulting complex. How well a guest molecule is accommodated depends upon its size and polarity, and the size of the particular cyclodextrin.

Cyclodextrins can be used: to catalyze organic reactions, often with regioselectivity and a degree of stereoselectivity; and, most important, as comparatively simple models by which to study the action of enzymes.

The effects of cyclodextrins on chemical reactions can arise in a number of ways.

(a) They can simply hide certain parts of a guest molecule and expose other parts.

(b) They can change the conformation of the guest.

(c) Their lipophilic lining provides a non-polar medium for the guest—but within a polar solvent.

(d) Their —OH groups can participate in the reaction: either directly—as bases and nucleophiles or as hydrogen-bonding sites—or via transient intermediates (esters, for example) formed by reaction with the host or with the attacking reagent.

The particular usefulness of cyclodextrins as enzyme models comes from the fact that, like enzymes (see, for example, Sec. 41.2), they first *bind* the substrate and then, through substituent groups, *act upon it*: clearly, an example of symphoria.

**Problem 39.18** The structure of cyclodextrins is shown, not only by x-ray analysis, but also by evidence of the kind we have already dealt with. Predict in detail the response expected from cyclodextrins to each of the following reagents or analyses: (a) Fehling's solution; (b) acidic hydrolysis; (c) methylation followed by acidic hydrolysis; (d) periodic acid; (e) molecular weight determination.

Cyclodextrins

Thomas Wimmer, Wacker-Chemie GmbH, Burghausen, Germany

*Ullmann's Encyclopedia of Industrial Chemistry*

DOI: 10.1002/14356007.e08_e02
Article Online Posting Date: January 15, 2003

3. Properties

Physical Properties. Selected physical properties of a-, b- and g-CD are listed in Table 1.

**Table 1. Physical properties of the most important cyclodextrins**

| | a-Cyclodextrin [10016-20-3] | b-Cyclodextrin [7585-39-9] | g-Cyclodextrin [17465-86-0] |
|---|---|---|---|
| Formula | $C_{36}H_{60}O_{30}$ | $C_{42}H_{70}O_{35}$ | $C_{48}H_{80}O_{40}$ |
| Molecular mass | 972.85 | 1135.00 | 1297.14 |
| Solubility in water (25 °C), g/100 mL | 14.5 | 1.85 | 23.2 |
| Crystal water, wt % | 10.2 | 13.2 – 14.5 | 8.13 – 17.7 |
| $[\alpha]_D^{25}$, ° | + 148 | + 162 | + 177 |
| *mp*, °C | > 200 °C | > 200 °C | > 200 °C |
| p$K_a$ value (25 °C) | 12.331 | 12.202 | 12.081 |

Cyclodextrins are insoluble in alcohols, ketones, ethers, chlorinated hydrocarbons, and aliphatic and aromatic hydrocarbons.

Chemical Properties [3]. Cyclodextrins are chiral, nonreducing oligosaccharides. Upon oxidation with periodate the glucose rings are cleaved; neither formic acid nor formaldehyde is produced. The only degradation product of all cyclodextrins in acidic solution is glucose. The hydrolysis rate follows the order g > b > a. Under acidic conditions cyclodextrins are hydrolyzed more slowly than maltooligosaccharides. The glycosidic bond in cyclodextrins is hydrolyzed by a-amylase but not by b-amylase. The rate of enzymatic hydrolysis is fastest with g-CD, followed by b-CD and a-CD. All cyclodextrins are very stable and highly soluble in alkaline solution (pH > 14). In fact the solubility in water can be highly increased in basic solutions. Under nitrogen atmosphere cyclodextrins are stable up to 250 °C [4].

Substitution of hydrogen of the primary and secondary hydroxyl groups leads to cyclodextrin derivatives. Most reactions are carried out in aqueous solutions (all mentioned in Fig. 4 except acetylations). Other suitable solvents are dimethyl sulfoxide, dimethyl formamide, and pyridine.